REMARKS

Applicants have amended claims 1, 40, 62, and 86 for purposes of clarity. No new matter has been added.

Claims 1, 2, 5-9, 17-24, 40, 44-46, 62, 66, 67, and 86-93 remain pending for examination.

Objections

Claims 1, 40, 62, and 86 have been objected to because the wording of these claims is "slightly confusing, particularly with regard to the preamble."

Applicants have amended these claims, as requested by the Patent Office. Applicants believe that these claims, as amended, flow more smoothly, although Applicants do not believe the claims as pending prior to amendment herein to be unclear or indefinite.

Rejections under 35 U.S.C. §103(a) in view of Wolfe, Ranganathan, The Online Medical Dictionary and IUBMB Enzyme Nomenclature

Claims 1, 2, 5-9, 17-21, 86-91, and 93 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Wolfe, *et al.*, "Orally ingested microencapsulated urease and an adsorbent, zirconium phosphate, to remove urea in kidney failure," *Int. J. Artificial Organs*, 10(4): 269-274, 1987 ("Wolfe") in view of Ranganathan, *et al.*, U.S. Pat. Apl. Pub. No. 2001/0051150 ("Ranganathan"), in light of the Online Medical Dictionary (believed to be http://cancerweb.ncl.ac.uk/cgi-bin/omd, accessed 2/28/05, cited in a prior Office Action) and "IUBMB Enzyme Nomenclature."

At the outset, Applicants do not appear to have received a copy of "IUBMB Enzyme Nomenclature" relied upon by the Patent Office (e.g., a copy of a chapter, a print-out of a web page, etc.), and thus are unable to concede to its accuracy. Applicants respectfully request a copy of this reference.

In summary, the Patent Office states that Ranganathan describes the necessary motivation to modify the teachings of Wolfe to also include isolated uricase and isolated creatininase. The Patent Office states that Wolfe teaches an oral delivery composition comprising a capsule comprising isolated urease given in conjunction with zirconium phosphate, although Wolfe does not teach or suggest uricase or creatininase. Ranganathan is relied on for the teaching that urea,

creatinine, and uric acid flow into the small intestine and equilibrate across the small intestine epithelium. According to the Patent Office, one of ordinary skill in the art would be motivated to make the modification to Wolfe because "the most effective treatment requires removal of all three toxins present in elevated concentrations in the gastrointestinal tract of such patients." The Patent Office also goes on to state that one would expect success because uricase and creatininase are both commercially available, and that one would not expect negative interactions between the three enzymes. Further, the Patent Office states that there would be a reasonable expectation of success since uricase and creatininase function similarly to urease by breaking down their respective toxins.

Applicants respectfully disagree that there would have been a reasonable expectation of success for the proposed combination. Wolfe is directed only to artificial, *in vitro* systems, and does not teach that such systems have any relevance to an *in vivo* system. Wolfe, in fact, teaches away from their use *in vivo*. For example, on p. 271-272, at the start of the Discussion section, Wolfe states that "It is not necessarily valid to infer that stirred batch studies are comparable to what happens in the intestine," and that "Diffusion of substrate and products into and out of the intestine may alter the picture completely." Wolfe also concludes on page 273, right column, that "The first question to ask is whether a gut urea clearance of 3 ml/min can really be attained *in vivo* within this system. *The definite answer cannot be given here.* What can be concluded is that the systems efficacy is not at all decreased in gut fluid and therefore is potentially useful in oral therapy [emphasis added]," and "The mathematical study does show that if clearances of 3 ml/min or greater were possible with a system presenting limited side-effects, considerable benefits could be drawn from the adjunctive use of the therapy." Thus, Wolfe does not disclose or suggest that their *in vitro* system could be used to predict an *in vivo* system, and at best, Wolfe merely suggests that microencapsulated urease, in conjunction with zirconium phosphate, is a combination that bears further study.

Ranganathan cannot be used to cure the deficiencies of Wolfe. Ranganathan is relied on to suggest that urea, creatinine, and uric acid flow into the small intestine and equilibrate across the small intestine epithelium. However, Ranganathan is only directed to microencapsulated sorbents (see, e.g., the Summary of the Invention, Paragraphs 0014 and 0015), and accordingly, Ranganathan does not teach that an encapsulated enzyme would be useful in an *in vivo* system.

Additionally, The Online Medical Dictionary and IUBMB Enzyme Nomenclature appear to be relied on only to show that uricase and creatininase were known to degrade uric acid and creatinine, respectively.

Accordingly, the combination of Wolfe and Ranganathan, in light of The Online Medical Dictionary and IUBMB Enzyme Nomenclature, would not lead one of ordinary skill in the art to make the combination proposed by the Patent Office, as there would be no reasonable expectation that such a combination would be successful. Wolfe only suggests a reasonable expectation of success in an *in vitro* system, and Ranganathan only suggests a reasonable expectation of success for the use of encapsulated sorbents. None of these references, taken singly or in combination, gives a reasonable expectation of success for the proposed combination.

Moreover, Wolfe teaches that zirconium phosphate should not be contained within the capsules ("It was proposed to test the feasibility of using the same combination of urease and ZP [zirconium phosphate], but to encapsulate the urease only and leave the ZP free," page 269, right column), whereas Ranganathan actually teaches the opposite, i.e., that sorbents should be contained within the capsule ("An object of the present invention is to provide microencapsulated and/or enteric coated compositions which comprise a mixture of sorbents with specific adsorption affinities...," Paragraph 0014). Thus, it is not clear how one of ordinary skill in the art would be able to even combine Wolfe and Ranganathan.

Thus, for at least these reasons, it is believed that independent claims 1 and 86 are patentable over Wolfe, Ranganathan, The Online Medical Dictionary, and IUBMB Enzyme Nomenclature, and it is thus respectfully requested that the rejection of these claims be withdrawn. Claims 2, 5-9, 17-24, and 87-93 each depend, directly or indirectly, from independent claims 1 or 86, and are believed to be allowable for at least the above-mentioned reasons. Withdrawal of the rejections of these claims is also respectfully requested.

Rejections under 35 U.S.C. §103(a) in view of
Wolfe, Ranganathan, Kominami, Sparks, and Smith

Claims 18-24 and 92 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Wolfe in view of Ranganathan, further in view of Kominami, *et al.*, U.S. Patent No.

4,240,376 ("Kominami"), Sparks, *et al.*, "Binders to Remove Uremic Waste Metabolites from the GI Tract," *Trans. Amer. Soc. Artif. Int. Organs*, 18:458-464, 1972 ("Sparks"), and Smith, *et al.*, U.S. Patent No. 4,857,555 ("Smith").

With respect to claims 18-24, these claims each depend, directly or indirectly, from independent claim 1, and are believed to be allowable for at least the above-described reasons. Moreover, it is not seen how the addition of Kominami, Sparks, or Smith with Wolfe and Ranganathan, teach all of the limitations of independent claims 1 or 86 (discussed above), let alone all of the limitations of dependent claims 18-24 and 92.

For instance, Kominami is generally directed to methods for keeping aquatic animals alive over long periods of time (see title), and it is not seen why one of ordinary skill in the art of oral drug delivery would turn to this reference. The Patent Office has not pointed to any disclosure or suggestion in either Wolfe or Ranganathan that would lead one of ordinary skill in the art to combine an encapsulated system with a method for keeping aquatic animals alive over a long period of time.

Sparks is generally directed to encapsulation of ingestible materials which can react with uremic toxins in the gastrointestinal tract, such as activated carbon. However, Sparks does not disclose or suggest encapsulating uricase or creatininase (or any other enzyme), and thus, it is not seen how Sparks can be used in conjunction with the other cited references in order to reach claim 18, which depends from claim 1.

Smith discloses a method for treating catabolic dysfunction (a physiological condition in which the degradation of an anatomical structure occurs; see col. 1, lines 23-25), but does not disclose or suggest treating uremic toxins. It is not clear why one of ordinary skill in the art of oral drug delivery would turn to this reference, and the Patent Office has not pointed to a teaching or suggestion in either Wolfe or Ranganathan that would lead one of ordinary skill in the art to consider this reference.

Accordingly, it is believed that the Patent Office has not provided a teaching or suggestion that would lead one of ordinary skill in the art to combine Wolfe and Ranganathan with Kominami, Sparks, and Smith. It is thus believed that this rejection is improper, and it is respectfully requested that the rejection of claims 18-24 and 92 be withdrawn.

Rejection under 35 U.S.C. §103(a) in view of Chang, Ranganathan, Yamamoto, Shigyo, The Online Medical Dictionary, and IUBMB Enzyme Nomenclature

Claims 40, 44, 45, 62, and 66 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chang, *et al.*, U.S. Patent No. 6,217,859 ("Chang") in view of Ranganathan, Yamamoto, *et al.*, U.S. Patent No. 5,627,065 ("Yamamoto"), and Shigyo, *et al.*, U.S. Patent No. 5,728,562 ("Shigyo") in light of The Online Medical Dictionary and IUBMB Enzyme Nomenclature.

The Patent Office states that Chang teaches encapsulating a genetically engineered microorganism such that the microorganisms are not released from the capsule, but the capsule does not impede mass transport of substances (such as urea) into the capsule to come into contact with the entrapped microorganisms. Ranganathan is relied on for the teaching that urea, creatinine, and uric acid flow into the small intestine and equilibrate across the small intestine epithelium. According to the Patent Office, one of ordinary skill in the art would be motivated to make the modification to Chang because it was known that uric acid, creatinine, and urea were present in elevated concentrations in the gastrointestinal tract of uremic patients. Shigyo and Yamamato are relied on to show that one of ordinary skill in the art would know how to transfect a microorganism with creatininase and uricase genes. The Patent Office also asserts that the choice of a host microorganism would be matter of design choice, and that any biocompatible bacteria would have been suitable. Finally, the Patent Office states that there would have been a reasonable expectation of success because one of ordinary skill in the art would have been able to select a suitable microorganism for transfection, as well as encapsulating the microorganism.

Applicants respectfully disagree that there would have been a reasonable expectation of success for the proposed combination, as the mechanism by which the *E. coli* in Chang reduces urea in the body is not described in Chang and is hence unclear. For instance, urease may be expressed and secreted by *E. coli*, and the secreted urease may interact with urea within the capsule, or the secreted urease may exit the capsule and interact with urea in the gastrointestinal tract. It is not clear that uricase and/or creatininase would show the same behavior. Another possibility is that urea is able to diffuse across the capsule, and across the plasma membrane of *E. coli*, where it reacts with urease internally. Yet another possibility is that urea is actively transported across the plasma membrane of *E. coli*, e.g., as a nitrogen source. It should be noted

that urea has a molecular size/molecular weight that is significantly smaller than either uric acid or creatinine (see, e.g., Fig. 1 of the instant application), and thus, it is not clear whether uric acid or creatinine can diffuse across the plasma membrane of *E. coli*, or whether active transport would be required, and if so, whether such active transporters exist within the plasma membrane of *E. coli*. Still another possibility is that the *E. coli* naturally degrades urea, and the urease gene within the *E. coli* in Chang may not have even been expressed. Chang does not disclose experiments in which non-genetically engineering *E. coli* were used; the controls in Chang are free, non-encapsulated genetically engineered *E. coli*. Accordingly, in the controls, the non-encapsulated *E. coli* may have been killed or inactivated through other processes, e.g., via interaction with degradation enzymes, while the encapsulated *E. coli* were protected from the degradation enzymes. Thus, it is not clear how much urease was expressed by the genetically engineered *E. coli*, or how such expression of urease could be controlled, and it is also not clear whether uricase and/or creatininase could be controlled to a similar degree, or even if transfection of uricase and/or creatininase into *E. coli* would exhibit a similar beneficial effect *in vivo*.

Thus, one cannot extrapolate the transport properties of urea across the plasma membrane to the transport of creatinine or uric acid across the plasma membrane. In fact, Yamamoto suggests on p. 4, lines 45-50 that urease is not externally expressed by *E. coli*, since the urease must be removed by lysing the cells (i.e., the cells are "demolished," e.g., by ultrasonication, mechanical disintegration with glass beads, a French press, or the action of surfactants, etc. to obtain a crude extract), thus suggesting that urea may be transported into the cells, e.g., through active or passive mechanisms. Accordingly, given this intracellular transport behavior for urea, the transport behavior of creatinine and/or uric acid, or the expression of uricase and/or creatininase, cannot reasonably be predicted.

In short, Chang does not lead one of ordinary skill in the art to conclude that the system in Chang could be easily adapted to other enzymatic systems without much further study and additional experimentation. Accordingly, Chang does not lead one of ordinary skill in the art to believe that the modification suggested by the Patent Office would have a reasonable expectation of success.

Ranganathan cannot be used to cure the deficiencies of Chang. As previously described, Ranganathan is relied on to suggest that urea, creatinine, and uric acid flow into the small intestine and equilibrate across the small intestine epithelium. However, Ranganathan only discloses use of a bacteria that metabolizes urea (Paragraph 0020, col. 3, lines 9-15), and does not disclose the use of bacteria transfected with uricase and/or creatininase. Yamamoto discloses a genetic sequence for creatinine amidohydrolase, but does not disclose or suggest a genetically engineered microorganism transfected with creatininase. Similarly, Shigyo discloses a genetic sequence for uricase, but does not disclose or suggest that a genetically engineered microorganism transfected with uricase can be used to treat uric acid internally. Additionally, The Online Medical Dictionary and IUBMB Enzyme Nomenclature appear to be relied on only to show that uricase and creatininase were known to degrade uric acid and creatinine, respectively. Accordingly, it is believed that the combination of Chang, Ranganathan, Yamamoto, Shigyo, The Online Medical Dictionary, and IUBMB Enzyme Nomenclature would not lead one of of ordinary skill in the art to conclude that the modification suggested by the Patent Office would have a reasonable expectation of success.

Moreover, the Patent Office has not pointed to a disclosure or a suggestion in any of the above-described references that would lead one of ordinary skill in the art to modify Chang in the manner suggested in the Office Action. The Patent Office states that it was known that urea, creatinine, and uric acid flow into the small intestine and equilibrate across the small intestine epithelium. However, it is not clear why such an observation would suggest to one of ordinary skill in the art to transfect the *E. coli* of Chang in a way that would additionally allow the *E. coli* to additionally produce creatininase and urease, in addition to urease. For instance, Chang does not teach or suggest that additionally transfecting *E. coli* with other genetic sequences encoding other enzymes would be useful or desired. Chang also does not teach or suggest the use of uric acid or creatinine. Instead, the Patent Office appears to make an assumption that one of ordinary skill in the art, in reading Chang and knowing that urea, creatinine, and uric acid equilibrate across the small intestine epithelium, would make the proposed modification. This would appear to be hindsight reasoning, as it is not clear why one of ordinary skill in the art would conclude that further genetic transfection of *E. coli* would be obvious, as opposed to other methods of

treating uric acid and creatinine, and the Patent Office has not pointed to a teaching or a suggestion in the prior art to make the proposed modification.

Furthermore, Applicants also supply a declaration from Michael J. Lysaght, one of the inventors, attesting to some of the points discussed above, for instance, whether there would have been a reasonable expectation of success for the proposed combination. Thus, for at least the above-mentioned reasons, it is believed that claims 40, 44, 45, 62, and 66 are patentable over Chang, Ranganathan, Yamamoto, Shigyo, The Online Medical Dictionary, and IUBMB Enzyme Nomenclature, and it is thus respectfully requested that the rejection of these claims be withdrawn.

Rejections under 35 U.S.C. §103(a) in view of Chang, Ranganathan, Yamamoto, Shigyo, Sparks, Wolfe, and Kominami

Claims 46 and 67 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chang in view of Ranganathan, Yamamoto, and Shigyo, further in view of Sparks, Wolfe, and Kominami.

Claims 46 and 67 depend from independent claims 40 and 62, respectfully, and are believed to be allowable for at least the above-described reasons. Moreover, it is not seen how the addition of Sparks, Wolfe, or Kominami with Ranganathan, Yamamoto, and Shigyo teaches all of the limitations of independent claims 40 or 62 (discussed above), let alone all of the further limitations of dependent claims 46 and 67.

As previously discussed, Kominami is generally directed to methods for keeping aquatic animals alive over long periods of time, and it is not seen why one of ordinary skill in the art of oral drug delivery would turn to this reference. Sparks is generally directed to encapsulation of ingestible materials which can react with uremic toxins in the gastrointestinal tract, such as activated carbon; however, Sparks does not disclose or suggest encapsulating cells, let alone transfected cells or cells able to express uricase or creatininase. Similarly, Wolfe is directed only to artificial, *in vitro* systems involving urease and zirconium phosphate (and not *in vivo* systems, as previously discussed), and does not teach or suggest transfected cells or cells able to express uricase or creatininase. Additionally, Chang does not disclose or suggest an ammonium update species.

Accordingly, it is not seen how the addition of Sparks, Wolfe, and Kominami to the combination of Ranganathan, Yamamoto, and Shigyo reaches all of the limitations of independent claims 40 or 62, from which claims 46 and 67 depend. Thus, it is believed that the Patent Office has not provided a *prima facie* case of obviousness for the rejection of claims 46 and 67, and it is respectfully requested that the rejection be withdrawn.

Conclusion

In view of the foregoing, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, that the application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge our Deposit Account No. 23/2825, under Order No. B0877.70025US00 from which the undersigned is authorized to draw.

Dated: May 25, 2006

Respectfully submitted,

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